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Editorial Comment

Defining the Role of Atrial Natriuretic Factor in Health And Disease*

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> No amount of experimentation can ever prove me right; a single experiment can prove me wrong.
>
> *(Albert Einstein)*

Historic perspective. Roach and coworkers (1) report in this issue of the Journal the results of an elegant and difficult investigation of the interaction between atrial natriuretic factor (ANF) and the cardiopulmonary baroreceptor reflexes in normal human subjects. These experiments were the natural outgrowth of the demonstration over the past several decades of the important role the atria play in both neuronal and hormonal regulation of cardiovascular homeostasis. A prominent role of the atria as sites for sensing changes in central blood volume was demonstrated by Henry et al. (2) in 1956 when they inflated a balloon in the left atrium of dogs and observed an increase in urinary flow rate. They theorized that the mechanism for this response involved a neurogenic reflex. In the 1960s, de Wardener et al. (3) suggested the existence of a circulating natriuretic substance based on data from cross-circulation experiments in dogs undergoing saline volume expansion. de Bold and colleagues (4) reported in 1981 that crude extract from atria infused into rats produced a 30-fold increase in both urinary sodium and chloride excretion with impressive but less striking increases in urinary flow rate and potassium excretion; the heart was established as an endocrine organ. The atrial substance was characterized as a peptide, which, together with its prohormone, was soon sequenced (5). The peptide hormone has variously been termed atrial natriuretic factor (ANF), atrial natriuretic peptide (ANP), atriopeptin, cardioatrin, auriculin and atrin. Atrial natriuretic factor has numerous biologic actions including natriuresis, vasodilation (particularly of preconstricted vessels), increase in renal blood flow and glomerular filtration rate and decrease in aldosterone production, renin release, thirst and vasopressin secretion (6).

The physiologic role of the "low pressure" cardiopulmonary baroreceptors (mechanoreceptors) in humans was clarified when Roddie et al. (7) reported in 1957 that an increase in central venous pressure achieved by passive leg raising increased forearm blood flow without altering systemic arterial pressure. Subsequent studies have demonstrated that the low pressure cardiopulmonary baroreceptors are the afferent source of an inhibitory reflex that governs sympathetically controlled blood flow to skeletal muscle (8). Low pressure cardiopulmonary baroreceptors are located prominently in both atria as well as in ventricular endocardium and the pulmonary circulation (8). In humans these baroreceptors regulate skeletal muscle blood flow with only a small influence on splanchnic blood flow, heart rate and renin and vasopressin release. In contrast, arterial ("high pressure") baroreceptors or mechanoreceptors greatly influence heart rate, splanchnic blood flow and renin and vasopressin secretion. Afferent information from both the cardiopulmonary and arterial baroreceptor systems is mediated through the central nervous system cardiovascular control centers, particularly in the medulla and hypothalamus (9).

Cardiovascular homeostasis is achieved by the orchestration of neural and hormonal systems. Thus, the proximity of the cardiopulmonary afferent receptors and ANF secretion sites and the perceived importance of these two mechanisms in intravascular volume control demanded that the potential for interaction of these two systems be explored. A sympathoinhibitory effect of ANF was suggested when its infusion into experimental animals did not produce the expected tachycardia despite reduction in systemic arterial blood pressure (10,11). Various studies supported the concept of ANF-induced sympathoinhibition (10–17). These studies generally involved doses of atrial natriuretic factor at the higher end of the dose-effect curve, that is, pharmacologic doses. The physiologic significance must not be disregarded because pharmacology may often represent exaggerated physiology.

Consideration of a neurally mediated role for ANF was fueled by the finding of the hormone at many potential sites for action. For example, ANF may either stimulate vagal afferents or enhance the activity of mechanosensitive atrial vagal fibers (11). Also, its binding sites are present in presynaptic nerves and circumventricular organs such as the subfornical organ and area postrema, areas important in cardiovascular control and accessible to circulating atrial natriuretic factor (18,19). To clarify the possible physiologic and pathophysiologic significance of these observations, Roach et al. (1) used ANF infusions at the lower end of the

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dose-effect curve (for blood concentrations in the pathophysiologic range) to study the effects of the hormone on the reflex response of selectively unloading the cardiopulmonary mechanoreceptors by carefully regulated lower body negative pressure. Efferent sympathetic nerve activity was measured directly. These authors concluded that ANF is unlikely to play a meaningful physiologic role in modulating cardiopulmonary baroreceptor system activity.

Caution concerning this conclusion is advised because under physiologic conditions ANF is released when cardiopulmonary mechanoreceptors are *loaded* (20,21), not unloaded. Thus, increased cardiopulmonary baroreceptor inhibitory input into cardiovascular control centers in the central nervous system, such as the hypothalamus and medulla, might influence the response to circulating ANF (9).

The action of ANF on neural reflex mechanisms may also depend on the status of the renin-angiotensin system. The peptide is an endogenous antagonist to angiotensin II (6). Binding sites of ANF and angiotensin II overlap in the brain, kidney and adrenal cortex (22). A potential site for interaction of ANF and the renin-angiotensin system in modulating autonomic reflexes is the area postrema. Both ANF and angiotensin II have binding sites in the area postrema; angiotensin II stimulates the area postrema to produce hemodynamic changes and modifies baroreceptor activity (23). A possible role for ANF in modulating cardiopulmonary baroreflexes needs to be studied under physiologic modifications of atrial stretch and alterations of the renin-angiotensin system. Such investigations will be aided by a specific ANF antagonist.

Clinical relevance. Studies such as the one reported by Roach et al. (1) are critical not only for understanding normal cardiovascular physiology, but also for understanding the pathophysiology of some diseases and for developing therapeutic strategies. Pathophysiologic states in which abnormalities in atrial natriuretic factor, cardiopulmonary baroreceptors and the renin-angiotensin system may coexist are congestive heart failure and primary systemic arterial hypertension.

In congestive heart failure, circulating ANF levels are increased (24) and may be viewed as a counterregulatory hormone providing a mechanism for vasodilation and salt and water loss in opposition to vasoconstriction and salt and water retention induced by activation of the renin-angiotensin-aldosterone and sympathetic nervous systems (25). Cardiopulmonary baroreceptor function is also abnormal in congestive heart failure and may contribute to excessive neurohumoral drive, with increased resistances in renal, splanchnic and forearm vascular beds (8). In congestive heart failure, increases in central blood volume and atrial stretch convey information to the central nervous system suggesting volume overload, and decreased activity by arterial baroreceptors and decreased renal perfusion indicate inadequate circulating blood volume. Thus, conflicting afferent information may be presented to the central nervous system. The counterregulatory importance of ANF in congestive heart failure is indicated by hemodynamic worsening in experimental animal models of congestive heart failure that are given ANF monoclonal antibodies (26). Infusion of ANF produces beneficial hemodynamic effects and salt and water loss in patients with congestive heart failure (27), although the effects may be blunted by down-regulation of atrial natriuretic factor receptors (28). Increasing concentrations of circulating atrial natriuretic factor may restore the balance between opposing systems (29). Notably, the angiotensin-converting enzyme inhibitor captopril restores the effectiveness of ANF in experimental congestive heart failure (30).

It is possible that ANF is involved in the pathophysiology of hypertension (31), particularly when plasma renin activity is low (32). Infusion of ANF has been found to reduce systemic arterial blood pressure in experimental hypertensive animals and in hypertensive humans. Cardiopulmonary baroreceptor responses may also be abnormal in hypertension, that is, more sensitive during early hypertension, with subsequent reduction as cardiac hypertrophy develops (33). Studies of hypertension development in the Dahl salt-sensitive rat (a low renin model of hypertension) indicate abnormality of cardiopulmonary baroreceptor function and ANF (34,35); the baroreflex impairment is aggravated by a high-salt diet (36). Therefore, as in congestive heart failure, the pathophysiologic interaction of ANF, cardiopulmonary baroreceptors and the renin-angiotensin system is apparent.

Clearly, the cardiopulmonary and arterial baroreceptor systems, atrial peptides and the renin-angiotensin-aldosterone systems interact to regulate blood volume and pressure; other factors or systems may await discovery. Much clinical value has been derived from investigation of the renin-angiotensin-aldosterone system; it is hoped that studies of the role of ANF in health and disease will yield similar dividends. However, the complexity of these factors requires that each pathophysiologic state be studied independently; extrapolation from normal subjects to subjects with disease may be misleading.

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